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Editorial Comment

Radionuclide Detection of Myocardial Ischemia and Myocardial Viability: Is the Glass Half Empty or Half Full?*

FRANS J. TH. WACKERS, MD, FACC

New Haven, Connecticut

Noninvasive cardiac imaging, either at rest or during stress, has been for many years an integral part of evaluating and managing patients with suspected or known coronary artery disease. In the present era, when appropriate use of resources is under heavy scrutiny, the use of noninvasive imaging modalities can be expected to increase, further serving as effective gatekeepers for triaging and directing patients toward appropriate management strategies (1). In this value-driven environment, radionuclide myocardial perfusion imaging will play an important role for two reasons: the ability to assess the functional significance of anatomic coronary artery disease and the ability to quantify such variables. In recent years the methodology of interpreting myocardial perfusion images has changed according to the clinical questions posed.

Stress testing in patients with coronary artery disease aims to reproduce a patient's symptoms and to elicit unequivocal objective evidence of myocardial ischemia. This is entirely dependent on the ability of a stress modality to achieve metabolic demand–supply imbalance and thus myocardial ischemia. There are multiple clinical reasons why this may not always be successful: lack of patient motivation, inability to exercise and inability to achieve appropriate work load.

Heterogeneity of myocardial blood flow without ischemia. The advantage of stress radionuclide imaging is that abnormalities on the perfusion image do not depend on provocation of true myocardial ischemia. The underlying principle of an abnormal response to radionuclide stress myocardial perfusion imaging is the creation of heterogeneity of regional myocardial blood flow because of differences in coronary blood flow reserve in vascular territories supplied by normal and stenosed coronary arteries. Elhendy et al. (2) in a recent issue of the Journal observed that 26% of patients with reversible single-photon emission computed tomographic (SPECT) myocardial perfusion defects had no evidence of myocardial ischemia (i.e., wall motion abnormalities on echocardiography) during the same dobutamine stress test. Heterogeneity of myocardial blood flow or regional myocardial hypoperfusion is known to precede metabolic evidence of myocardial ischemia and regional contraction abnormalities. Elhendy et al. (2) hypothesized that in patients with (false) negative dobutamine stress echocardiographic results, the achieved level of stress or the quantitative extent of scintigraphic abnormalities, or both, would be less than that in patients with ischemic wall motion abnormalities. Indeed, the stress rate-pressure product was lower in these patients, but no difference was seen in the extent or severity of reversible myocardial perfusion abnormalities. This finding is consistent with the concept that myocardial blood flow heterogeneity, extensive or not, is not necessarily temporally associated with provoked ischemia. Thus, stress myocardial perfusion imaging can be expected to detect significant coronary artery disease earlier than techniques that depend on provocation of ischemia.

Quantification of ischemic burden. Another strength of radionuclide myocardial perfusion imaging is the widespread use of computer quantification of relative myocardial radiotracer uptake. This quantification can readily be done because radionuclide images are inherently quantitative: The number and location of scintillations detected by the gamma camera are stored in a computer matrix. Image quantification can be performed using either bull's-eye or circumferential profile analysis. Using both approaches, a patient's relative myocardial radiotracer uptake is quantitatively compared with that from normal data files, representing the lower limits of normal radiotracer distribution (3,4). This comparison allows for objective and, importantly, reproducible quantification of stress-induced regional myocardial perfusion abnormalities, as well as quantification of defect reversibility. The latter allows for quantitative assessment of the degree and extent of coronary flow heterogeneity, which relates to the functional significance of angiographic coronary artery disease and the potential "total ischemic burden" if true ischemia were to be provoked. The extent of perfusion abnormalities has been shown to be associated strongly with patient outcome (5,6). The larger the exercise-induced myocardial perfusion abnormality, defect reversibility and extent of rest perfusion defect, the more the patient's prognosis is likely to be compromised by the occurrence of a future cardiac event. It is therefore important in clinical practice to report the quantitative extent of stress-induced myocardial perfusion abnormalities.

Elhendy et al. (2) used quantitative technetium-99m sestamibi dobutamine stress SPECT imaging to quantify the extent of myocardial ischemia. They did not necessarily assess and quantify the extent of myocardial ischemia; rather, they quantified the extent of the dobutamine-induced blood flow heterogeneity. These scintigraphic abnormalities were in ~25% of patients not associated with true myocardial ischemia and dobutamine-induced echocardiographic wall motion abnormalities.

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From the Departments of Diagnostic Radiology and Medicine, Yale University School of Medicine, New Haven, Connecticut.

Address for correspondence: Dr. Frans J. Th. Wackers, Departments of Diagnostic Radiology and Medicine, Yale University School of Medicine 333 Cedar Street, P.O. Box 208042, New Haven, Connecticut 06520-8042.

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Myocardial viability, a quantifiable continuum. Radionuclide myocardial perfusion imaging at rest is increasingly used to assess myocardial viability (7). This assessment is of particular clinical relevance in patients with known coronary artery disease and left ventricular dysfunction who are considered for coronary revascularization. For the purpose of determining myocardial viability, image analysis is to be focused differently than that for stress myocardial perfusion imaging. It is not relevant to assess whether a certain myocardial segment has less radiotracer accumulation, but how much radiotracer is actually accumulated. The glass is not to be viewed as half empty (as is appropriate for stress myocardial perfusion imaging), but as half full. For assessment of myocardial viability, considerable emphasis has been placed on the amount of rest radiotracer uptake (8). As mentioned before, quantification of relative myocardial radiopharmaceutical uptake can readily be obtained using available computer software. Clinical studies comparing rest thallium-201 uptake with evidence for active myocardial metabolism by positron emission tomographic imaging or improvement of regional wall motion after revascularization, or both, have established the notion that a threshold exists below which myocardial revascularization is apparently not useful. The concept that myocardial segments containing at least 50% of normal thallium-201 uptake are viable and are appropriate targets for coronary revascularization is now widely accepted. As a corollary, myocardial segments with <50% of normal thallium-201 uptake are generally thought to be scar tissue that would not benefit from revascularization. However, this reasoning is an oversimplification of issues related to myocardial viability and the usefulness of revascularization. Infarctions are often not complete and may be nontransmural. As long as some amount of viable myocardium is present in a myocardial segment, depending on the ratio of the mixture of viable to nonviable cells, myocardial imaging with agents that track myocardial viability may show slightly, moderately or markedly decreased radiotracer uptake on tomographic images. The aforementioned 50% threshold of radiotracer uptake relates to the likelihood that regional wall motion in such a segment improves after revascularization. However, although improvement in regional function is a rewarding result of revascularization, the most common purpose of revascularization is the relief myocardial ischemia. Myocardial segments with <50% of normal radiopharmaceutical uptake may contain viable cells that potentially may become ischemic during stress and ultimately may infarct. It is not unusual to observe partially reversible myocardial perfusion defects in areas with severely reduced (<50% of normal) rest radiotracer uptake. Revascularization of such segments is not meaningless, although it may not be associated with improved regional wall motion.

To make such assessments about a patient's myocardial status, quantification of myocardial perfusion images is important. Furthermore, an understanding of the characteristics of radiotracers is important. The unique properties of thallium-201 for assessing myocardial viability are well documented. New technetium-99m–labeled myocardial perfusion imaging agents, such as sestamibi, have significantly improved the quality of SPECT myocardial perfusion imaging. However, because the mechanism of myocardial uptake of sestamibi differs from that of thallium-201, the reliability of this agent as a marker of myocardial viability has been questioned, in particular, under conditions of low rest myocardial blood flow (9). Kauffman et al. (10) in this issue of the Journal, demonstrate quantitatively that rest regional myocardial uptake of sestamibi in patients with ischemic regional left ventricular function is comparable to that of thallium-201. Nevertheless, in individual patients, thallium-201 and sestamibi images were not always identical. Using 50% of normal radiotracer uptake as a threshold, discordance occurred in 12% of patients. This threshold for myocardial viability is an empirically determined cutoff value. Myocardial viability should instead be viewed as a continuum. There is probably no true clinical difference between segments that are measured as having, for example, 51% versus 45% of normal radiotracer uptake. Moreover, due to physical differences between thallium-201 and technetium-99m, images obtained of the same object are not identical. For instance, a given perfusion defect may be quantitatively less severe on a scintigraphic image obtained with thallium-201 than on one obtained with sestamibi because of the larger amount of low energy scatter with thallium-201. It is therefore important to consider the quantitative methodology used in the study by Kauffman et al. (10). Rather than using circumferential profiles of tomographic slices that allow for detailed segmental comparisons in individual patients, which is appropriate when comparing stress–rest uptake, average values in relatively large bull's-eye map segments were used that "smooth out" relatively small and clinically insignificant differences between the two radiotracers. Using this averaging approach, no statistical difference was seen between segments with mildly and severely reduced rest thallium-201 and sestamibi uptake. These observations provide a further scientific basis to the growing clinical experience that rest sestamibi myocardial perfusion imaging can be used successfully for quantitative assessment of myocardial viability.

Both studies (2,10) illustrate that radionuclide myocardial perfusion images should not be interpreted in a binary fashion: normal or abnormal, viable or scar. Computer quantification of radionuclide myocardial perfusion images allows a more sophisticated approach: on the one hand, quantitative assessment of heterogeneity of coronary flow reserve, and on the other, quantification of the amount of residual viable myocardium.

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JACC Vol. 27, No. 7
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